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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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NASA JOHNSON SPACE CENTER
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2101 NASA RD 1
HOUSTON TX 77058

EXAMINER

LARSON, T

ART UNIT

PAPER NUMBER

1635

DATE MAILED:

06/11/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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Office Action Summary

Application No.

09/532,001

Applicant(s)

GOODWIN ET AL.

Examiner

Thomas G. Larson, Ph.D.

Art Unit

1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-12 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-3, 5 and 7-12 is/are rejected.
- 7) ☒ Claim(s) 4 and 6 is/are objected to.
- 8) ☐ Claims ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- 15) ☒ Notice of References Cited (PTO-892)
- 16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____.
- 18) ☐ Interview Summary (PTO-413) Paper No(s). ____.
- 19) ☐ Notice of Informal Patent Application (PTO-152)
- 20) ☒ Other: *Notice to Comply w Seq. Rules*.

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

A paper copy of the sequence listing has been provided, but an electronic copy in computer readable format has not. It is recommended that applicant request that the computer readable copy of the sequence listing be transferred from the parent application.

Applicant is given until the date a response is due to this communication within which to comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

2. It is recommended that all continuing data, including the reference to provisional application 60/043205, be consolidated into a single first paragraph.

The reference to the provisional application is found at lines 14-15 of the first page and should be moved to the first paragraph.

3. An information disclosure statement has not been made of record in this application at the time of this communication. If applicant wishes for an information disclosure statement to be considered, it is suggested that appropriate action be taken to insure that it is made of record before the issuance of the next Office action.

4. The abstract of the disclosure is objected to because does not describe the claimed subject matter. It is suggest that the abstract be revised to include a brief description of the SSRE decoy and the method of using it to induce protein expression. Correction is required. See MPEP § 608.01(b).

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 11 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Khachigian et al.

The claims are drawn to an oligonucleotide comprising the sequence GAGACC or GGTCTC.

Khachigian et al. teach oligonucleotides comprising the SSRE and the binding of a transcription factor to the SSRE in an extract from a cells exposed to shear stress (Fig. 1A).

Although the claims recite the intended use and function as a transcription factor decoy, these limitations do not distinguish over the prior art. The recitation of an intended use does not carry patentable weight if it does not result in a structural difference from the prior art composition (MPEP 2111.02) and if all structural limitations are met, all functional limitations are presumed to be present (MPEP 2112.01).

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-3, 5, and 7-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inducing expression in cells or tissues cultured *in vivo*, does not reasonably provide enablement for inducing expression in cells *in vivo* in a whole organism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to make and/or use the invention commensurate in scope with these claims.

In *In re Wands* (8 USPQ 2d 1400, 1404; also see *Ex parte Forman*, 230 USPQ 546), the issue of enablement in molecular biology was considered and the factors to be considered in a determination of "undue" experimentation were summarized. These factors include (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of skill of those in the art; (e) the predictability of the art; (f) the amount of direction or guidance presented; (g) the presence or absence of working examples; (h) the quantity of experimentation necessary. See MPEP § 2164.01(a).

The claims broadly embrace the induction of a protein in a cell in an unspecified context comprising contacting the cell in an unspecified manner with a decoy oligonucleotide comprising an SSRE. With the exception of claim 5, the cell is an unspecified, generic cell. With the exception of claim 9, the expressed protein is an unspecified, generic protein. The context of the cell is unspecified, but as evidenced by claim 4, the scope of the claim is not limited to a cell cultured *in vitro*. Therefore, the scope of the claim also embraces a cell *in vivo* in a whole organism. However, it is unclear how the cells in the whole organism are to be contacted with the oligonucleotide decoy as provided for by the method steps of the claim. Moreover, contacting cells in a whole organism with an oligonucleotide would embrace the therapeutic application of the method.

The successful therapeutic application of oligonucleotide compounds was unknown in the art at the time the application was filed. For example, Stull et al. teach that the development of nucleic acid therapeutics is impeded by "several formidable obstacles...(that) require improving the stability of polynucleotide drugs in biological systems, optimizing the affinity and efficacy of the drug without reducing its selectivity, and targeting and delivering nucleic acids across cell membranes" (p. 476, col. 1, second full ¶). Stull et al. further state that "the delivery and entry of nucleic acid drugs into the target site remains a major obstacle to the successful introduction of this aspect of the molecular biology revolution into a clinical setting" (p. 478, col. 1 first full ¶). Gewirtz et al. teach that a "major problem in this field is the ability to deliver ODN (oligodeoxynucleotides) into cells and have them reach their targets" (p. 3161, col. 3, lns. 6-10). Rojanasakul teaches that the effective use of oligonucleotide therapeutics "has been limited due to several problems.... (B)ecause of their large size and charge, these compounds are poorly taken up by cells and therefore may not reach their target site. Moreover, problems associated with cellular targeting and affinity...to the target site pose major challenges to the successful utilization of these compounds" (abstract, lns. 8-13). Jen et al. also teach that the problem of delivery is one of the major obstacles to the therapeutic application of antisense compounds (p. 131, col. 2, ¶ 2, to p. 314, col. 1, ¶ 3). Jen et al. state that "some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable" (p. 313, col. 2,

¶ 2, last sentence). Jen et al. further state that "(g)iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive" (p. 315, col. 2, lns. 7-9).

Regarding the predictability of the art, the outcome of experiments involving biological or physiological systems is generally regarded as unpredictable. The problematic reproducibility of data and the poor correlation of the results obtained in cell culture with the results obtained in a whole organism are well-known problems in the art (see Antisense '97, p. 522, col. 1, 1st and 2nd full ¶s, for example). In the specific case of nucleic acid-based therapeutics, Gewirtz et al. teach that the results obtained from experiments involving the application of oligonucleotide-based compounds to inhibit physiological activities frequently produce results that were "highly variable", "non-informative", "misleading", or "unreproducible" (p. 3161, col. 2, 1st full ¶).

The level of skill in the art is extremely high with the skilled artisan generally having a Ph.D., and M.D., or both a Ph.D. and an M.D., together with several years of postdoctoral research experience. However, in spite of this high level of skill, the therapeutic application of nucleic acids has remained a relatively undeveloped art, as discussed above.

With regard to the amount of direction or guidance presented, the specification appears to be silent concerning the delivery and targeting of oligonucleotides in whole animals or in therapeutic applications. Thus, the

specification does not address the hurdles to the successful delivery of oligonucleotide compounds in whole animals or in therapeutic applications that are well known in the art, as evidenced by the teachings of the documents cited above.

Regarding the presence or absence of working examples, no examples, working or prophetic, are provided for the invention *in vivo* in a whole animal for therapeutic or any other purpose.

The amount of experimentation required to practice the claimed invention would be extensive in view of the breadth of the claims, the undeveloped state of the art, and the generalized nature of the guidance provided by the disclosure. The required experimentation would include developing methods of administration for oligonucleotide compounds that overcome the obstacles to the successful delivery of the compounds to the site of action in a whole animal. Such experimentation would necessarily be of a trial-and-error nature in view of the unpredictability of the art and the lack of appropriate examples. Such experimentation can not be considered routine in nature.

Therefore, in weighing the factors to be considered in determining whether or not the practice of a claimed invention would require "undue" experimentation, as set forth in *In re Wands* (8 USPQ 2d at 1404), the weight of the analysis clearly favors a finding of "undue" experimentation. See MPEP § 2164.01(a), last ¶. Since the skilled artisan could not have practiced the claimed invention without engaging

in undue experimentation, the specification fails to provide a disclosure that is commensurate with the scope of the claims.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 recites a concentration range, but the units associated with the numbers are for length rather than concentration. It is recommended that the units mM (millimolar) and nM (nanomolar) be used rather than mm (millimeter) and nm (nanometer), if that is what is intended.

11. Claims 4 and 6 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

12. Since allowable subject matter has been indicated, applicant is encouraged to submit formal drawings in response to this Office Action. The early submission of formal drawings will permit the Office to review the drawings for acceptability and

to resolve any informalities remaining therein before the application is passed to issue. This will avoid possible delays in the issue process.

13. Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The FAX numbers are (703) 308-4242 and (703) 308-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Unofficial papers, such as draft responses, may be transmitted to the examiner directly at (703) 305-7939. It is recommended that the examiner be notified when a fax is sent to this number.

Any inquiry concerning this communication or earlier communications should be directed to Thom Larson, whose telephone number is (703) 308-7309. The examiner normally can be reached Monday through Friday from 9:00 AM to 5:30 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

Thomas G. Larson, Ph.D.
Examiner

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Notice to Comply	Application No. 09/532,001	Applicant(s) Goodwin et al	
	Examiner T. Larson	Art Unit 1635	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- ☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- ☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- ☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- ☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- ☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- ☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- ☐ 7. Other:

Applicant Must Provide:

- ☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
(May be transferred from parent)
- ☐ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- ☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216

For CRF Submission Help, call (703) 308-4212

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